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Keywords
Electroencephalogram · Neurodevelopmental outcome · Newborn brain

Abstract
Background: Amplitude-integrated electroencephalography (aEEG) is used increasingly in neonatal intensive care and seems helpful in predicting outcomes at the age of 2 years. ***Objectives:*** To determine whether early aEEG patterns in preterm infants are equally useful in predicting outcomes at early school age. ***Methods:*** We recorded aEEG in 41 preterms (gestational age 26.0–32.9 weeks) at a median postnatal age of 9.7 h (IQR 7.0–25.3) and in 43 preterms on median day 8 (IQR 7–9). We assessed aEEG by pattern recognition and calculated the means of the aEEG amplitude centiles. At a median of 7.39 years, i.e., early school age, we assessed their motor, cognitive, and behavioral outcomes. ***Results:*** Depressed aEEG patterns were not associated with poorer outcomes. Cyclicity directly after birth was associated with a higher total IQ (mean 104 vs. 97, $p = 0.05$) and higher scores on visual perception (mean percentile 57.1 vs. 40.1, $p = 0.049$) and visual memory (mean percentile 34.5 vs. 19.1, $p = 0.090$). We found some associations between the aEEG amplitude centiles and cognitive outcomes, but none for motor or behavioral outcomes. There was an increased risk of abnormal scores on long-term verbal memory in cases of the lower 5th and 50th aEEG amplitude centiles directly after birth. The odds ratios were 0.65 (95% CI 0.42–0.99, $p = 0.040$) and 0.71 (95% CI 0.52–0.96, $p = 0.025$), respectively. ***Conclusions:*** In relatively healthy preterm infants the value of aEEG in predicting neuropsychological outcomes at early school age is limited. The presence of cyclicity directly after birth tends to be associated with better cognition.

Introduction

Preterm birth remains a major contributor to infant mortality and long-term morbidity, with about 50% of very-low-birth-weight infants suffering minor disabilities [1]. It is important to find early diagnostic methods that can reliably predict long-term outcomes to enable us to identify the infants at the greatest risk of neurodevel-

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opmental problems. This information is needed to adequately inform parents, to assist in managing care in general, and to indicate possible future neuroprotective interventions.

A reliable method to assess brain function is amplitude-integrated electroencephalography (aEEG). In contrast to its predictive value in full-term asphyxiated infants, the predictive value of aEEG is less clear in preterm infants [2]. In the latter, aEEG are predominantly discontinuous and change with increasing gestational age (GA), which makes it difficult to distinguish normal from abnormal patterns. Cyclic variations in aEEG, which suggest sleep-wake cycling, become obvious from 26 to 27 weeks of gestation, and from 29 to 30 weeks cyclicity is well developed [3]. Thus, the emergence of cyclicity, corrected for GA, can possibly serve as a suitable biomarker for functional outcome.

Wikström et al. [4] showed that a depressed aEEG in the first 24 h after preterm birth is associated with a poorer outcome at 2 years of age. Klebermass et al. [5] also reported that abnormal aEEG during the first 2 weeks after birth are associated with adverse outcomes at 3 years of age.

Studies in preterm infants that investigate the relationship between aEEG patterns and outcomes are scarce, and follow-up is usually relatively brief. To date, the value of early aEEG in predicting neurodevelopmental outcomes at school age is unknown. Our aim was therefore to explore whether early aEEG in very preterm infants are useful in predicting outcomes at school age. In addition, we assessed whether a more quantitative analysis of aEEG, in addition to pattern recognition, has an added value in predicting outcomes. We hypothesized that the absence of cyclicity and a more depressed aEEG background are associated with a poorer outcome.

Methods

We performed an explorative follow-up study at the University Medical Center Groningen, The Netherlands. Infants were admitted between 2004 and 2006 and participated in a prospective observational study using early aEEG. Because the availability of the cerebral function monitor (CFM) was limited, the cohort consisted of 71 infants with a GA of 26–32 weeks. Exclusion criteria were death, intraventricular hemorrhage (IVH) exceeding grade 2 according to Volpe [6], and chromosomal/congenital abnormalities. Five infants died, 9 had a large IVH, and the parents of 10 children declined the invitation to participate in the follow-up study. One infant was excluded because of hepatoblastoma, which was treated with chemotherapy. One child was lost to follow-up. The final cohort thus consisted of 45 infants. One infant had cerebral palsy, with a GMFCS score of more than 2 [7]. This particular infant could not be tested for cognition, but its motor outcome was assessed.

This study was approved by the medical ethics committee of the University Medical Center Groningen, and we obtained parental informed consent.

aEEG Recordings

The first aEEG recordings were made as soon as possible after birth and, if possible, repeated after 1 week. Due to the limited availability of the CFM, in some cases the first aEEG were performed during the second week after birth. We used a digital CFM that was not commercially available at the time of this study [8]. The CFM facilitates computing of aEEG amplitude centiles. The aEEG electrodes (neonatal ECG electrodes, Neotrode II; Conmed, Utica, NY, USA) were placed on positions P3 and P4 in accordance with the international 10/20 system.

The aEEG processor comprised a signal-shaping filter, a semilogarithmic rectifier, a peak detector, and a smoothing filter. Its hardware characteristics are identical to those of the CFM constructed by Maynard et al. [9]. The aEEG were displayed at a speed of 6 cm/h [9]. In an effort to obtain more information, we computed and displayed the means of the aEEG amplitude and the mean peak and mean trough values. All values were filtered by boxcar averages with a time window of 60 s. These mean peak and trough values represented the 5th and 95th centiles of the aEEG amplitude. We used a digital DC common average reference amplifier (Porti-X by TMSi; Enschede, The Netherlands) comprising a high input impedance (>2 GΩ) and a 22-bit sigma-delta analog-to-digital converter with a resolution of 0.0715 μV/bit and a sample frequency of 500 Hz. Low frequencies (<0.5 Hz) and high frequencies (>25 Hz) were attenuated by first-order high- and low-pass filtering. The aEEG were subsampled at 200 Hz and stored on a hard disk and processed at this subsample frequency.

aEEG Assessments

An expert in aEEG assessment assessed the aEEG based on Hellström-Westas and Rosén [10] as follows: continuous normal voltage, discontinuous normal voltage, burst suppression (BS), continuous low voltage, and flat tracing. Subsequently, cyclicity and epileptic activity (EA) were determined. Cyclicity was determined on the basis of sinusoidal variations in the aEEG background and included imminent sleep-wake cyclicity, characterized by cyclic variations of the lower border of the amplitude [10]. In addition to assessment by pattern recognition, the mean 5th, 50th, and 95th aEEG amplitude centiles for the duration of the recording period (mean 213 min) were calculated [8]. Before calculating the aEEG amplitude centiles, artifacts were rejected. The amplitude centiles were subsequently calculated for the epochs between the periods of cyclicity.

Follow-Up

Follow-up consisted of neuropsychological tests to assess motor, cognitive, and behavioral outcomes. Testing was supervised by a child neuropsychologist. The age of testing ranged from 6 to 8 years (median 7 years and 3 months).

Motor Outcome

The motor outcome was assessed with the Movement ABC. The total score is based on subscores for manual dexterity (fine motor skills), ball skills, and static and dynamic balance (coordina-

tion). A higher score indicates a poorer motor performance [11]. In addition, the parents completed the Developmental Coordination Disorder Questionnaire for possible motor and coordination problems [12].

Cognitive Outcome

To assess total, verbal, and performance intelligence, we used a shortened version of the WISC (ed 3, Dutch version) [13]. IQ were classified as normal (IQ ≥85), subclinical (IQ 70–85), or clinical (IQ <70). To assess selective attention and attention control, we used the subtests of the TEACH [14]. Verbal learning and memory were assessed with a standardized Dutch version of Rey's AVLT [15]. Visual memory, visuomotor integration, and central visual perception were assessed with the subtests of the NEPSY-II [16]. To assess executive functioning, we used the Dutch version of the parent-rated BRIEF [17].

Behavioral Outcome

To assess the behavioral outcome, parents completed the CBCL [18], the Children's Inventory of Social Behavior questionnaire [19], and the parent-rated ADHD questionnaire [20].

Clinical Variables as Potential Confounders

We accounted for GA, postnatal age in hours after birth at the first recording, sex, the 5-min Apgar score, IVH grades 1 and 2, sepsis, umbilical cord pH, use of morphine, and mechanical ventilation because these factors are known to influence aEEG and outcomes [8, 21].

Statistical Analysis

We used IBM SPSS statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) for all analyses. First, we used the Kolmogorov-Smirnov test to determine which variables were normally distributed. We categorized the children according to their functional neurological and developmental outcomes. For the Movement ABC and cognitive tests we used the percentiles on the standardization samples to classify the raw scores into normal (>15th percentile), subclinical (6th to 15th percentile), and clinical (≤5th percentile). For the questionnaires, we used a classification in accordance with the criteria in the various manuals.

We assessed differences in continuous outcome measures between the different aEEG background patterns and the presence of cyclicity per recording using the *t* test or the Mann-Whitney *U* test where appropriate. Because the aEEG background patterns in preterm infants are predominantly discontinuous, we combined continuous normal voltage and discontinuous normal voltage and compared it to BS.

To determine the relationship between the aEEG centiles and the outcome measures, we calculated Pearson correlation coefficients or, in the case of a nonnormal distribution, Spearman rank correlation coefficients. We adjusted for confounders, i.e., those clinical variables that were associated with aEEG centiles with a $p < 0.10$, using stepwise backward multivariate linear regression analyses in the case of a normal distribution and Spearman partial correlation test analyses in the case of a nonnormal distribution.

Next, a multivariate logistic regression model was used to calculate odds ratios (OR); to determine the value of aEEG amplitude centiles in predicting abnormal versus normal outcomes, we defined abnormal as subclinical and clinical taken together. In order to obtain sufficient power for the analyses, we selected those outcome variables on which the performance of more children was abnormal than expected (>15%). Again, we adjusted for confounders. $p < 0.05$ was considered statistically significant for all of the analyses. As our study was explorative, we did not perform statistical corrections for multiple testing.

Table 1. Patient characteristics

Characteristic	Value
Male/female ratio	22/23
Gestational age, weeks	29.0 (26.0–32.9)
Birth weight, g	1,245 (635–2,010)
Asphyxia	
Apgar score at 5 min	8 (1–10)
Umbilical cord pH	7.21 (6.54–7.38)
Ventilatory support	
None/low flow	1 (2)
CPAP	21 (47)
IPPV/HFO	23 (51)
Use of morphine	3 (7)
Continuously	1 (33)
At the time of intubation	2 (67)
Clinical seizures	0 (0)
Sepsis	12 (27)
CNS	9 (20)
Other	3 (7)
Cerebral pathology	
Intracranial hemorrhage grade 1–2	2 (4)
Periventricular leukomalacia grade 1	7 (15)

Data are expressed as medians (range) or numbers (%) unless otherwise stated. CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; HFO, high-frequency oscillation; CNS, central nervous system.

Table 2. Features of aEEG recordings in preterm infants

Feature	Postnatal age, days	
	0–2 ($n = 41$)	6–13 ($n = 43$)
Background pattern		
CNV	1 (2)	6 (14)
DNV	18 (44)	32 (74)
BS	22 (54)	5 (12)
Presence of cycling	28 (68)	38 (88)
Presence of EA	1 (2)	1 (2)
Amplitude centiles, μV		
Mean p5	5.1 (1.9–11.3)	6.6 (3.9–16.0)
Mean p50	10.8 (6.6–21.7)	13.0 (8.9–52.1)
Mean p95	36.1 (18.7–51.5)	38.1 (21.2–123.5)

Data are expressed as medians (range) or numbers (%). aEEG, amplitude-integrated electroencephalography; CNV, continuous normal voltage; DNV, discontinuous normal voltage; BS, burst suppression; EA, epileptic activity.

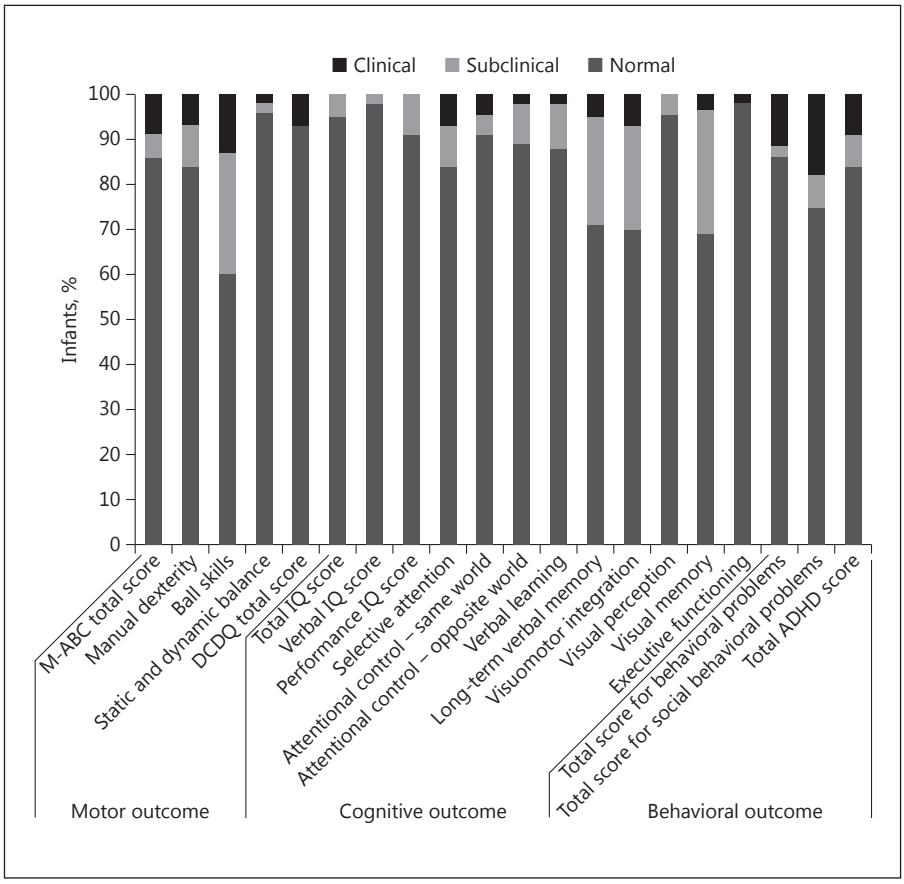

Fig. 1. Motor, cognitive, and behavioral outcomes in preterm infants, classified as normal, subclinical, and clinical.

Results

Patient characteristics are shown in Table 1. Only 1 neonate received morphine continuously during the first 48 h, which included the recording. None of the mothers had received sedatives of any kind.

aEEG Recordings

In 41 children an aEEG recording was made within the first 2 days after birth (median 9.7 h, IQR 7.0–25.3). This we defined as directly after birth. A second aEEG was recorded in 43 children (median day 8, IQR 7–9). The characteristics of the aEEG in relation to postnatal age are shown in Table 2.

The percentage of infants with BS decreased from 54% during the first recording to 12% during the second. In addition, the presence of cyclicity increased from 68 to 88%.

The mean 5th and 50th aEEG centiles increased significantly during the first week after birth ($p = 0.001$ and $p = 0.003$, respectively).

Outcome at School Age

The mean total IQ was 102 (SD 10.0), the mean verbal IQ was 103 (SD 12.2), and the mean performance IQ was 99 (SD 12.9). Figure 1 shows an overview of the proportions of the children's motor, cognitive, and behavioral scores.

Background Pattern of the aEEG in Relation to Outcomes

The average score on each outcome variable per aEEG background pattern is shown in Table 3a.

First Recording

Although some associations were found between the first aEEG and cognitive and motor outcomes, none of these reached statistical significance. In the case of BS, scores on verbal learning (percentiles: 64.7 vs. 48.6, $p = 0.068$) were better, as were the scores on ball skills (raw scores: median 2.0 [percentiles 25–75: 0.5–3.8] vs. median 3.0 [percentiles 25–75: 2.0–4.5], $p = 0.099$). In addition, scores on visual memory were higher in the case of

Table 3. Neurodevelopmental outcome scores

a Neurodevelopmental outcome scores per predominant aEEG background pattern per recording

Outcome score	First recording			Second recording		
	BS (*n* = 22)	DNV or CNV (*n* = 19)	*p*	BS (*n* = 6)	DNV or CNV (*n* = 38)	*p*
Motor outcome						
Movement ABC total score[c]	41.9 (26.1)	39.7 (26.0)	0.794	54.2 (20.4)	39.7 (25.1)	0.225
Manual dexterity[f]	1.5 (0.5–4.5)	1.5 (0.0–4.0)	0.688	1.0 (0.5–1.8)	1.8 (0.5–4.1)	0.345
Ball skills[f]	2.0 (0.5–3.8)	3.0 (2.0–4.5)	0.099[b]	2.0 (1–4.8)	2.8 (1–4.5)	0.840
Static and dynamic balance[f]	0.0 (0.0–1.8)	0.0 (0.0–1.0)	0.646	0.0 (0.0–0.8)	0.5 (0.0–1.5)	0.286
DCDQ 2007 total score[d]	65.4 (6.7)	63.8 (8.6)	0.728	65.2 (4.2)	64.8 (7.7)	0.755
Cognitive outcome						
Total IQ score	100.1 (9.1)	102.3 (10.7)	0.497	101.0 (10.7)	101.3 (10.6)	0.952
Verbal IQ score	104.3 (11.0)	99.7 (12.1)	0.222	102.9 (14.4)	102.8 (12.5)	0.980
Performance IQ score	95.9 (9.9)	103.3 (15.3)	0.082[b]	99.2 (10.8)	99.3 (13.5)	0.976
Selective attention[c]	36.8 (27.9)	42.5 (26.3)	0.452	22.3 (14.7)	42.4 (26.6)	0.078[b]
Attentional control						
Same world[c]	52.8 (29.5)	54.5 (29.3)	0.711	59.0 (27.1)	54.6 (29.9)	0.828
Opposite world[c]	45.5 (32.6)	44.0 (24.0)	0.672	58.2 (40.9)	43.6 (27.8)	0.412
Verbal learning[c]	61.8 (33.1)	48.6 (27.6)	0.131	61.5 (35.1)	57.1 (31.9)	0.875
Long-term verbal memory[c]	54.3 (31.8)	44.4 (32.6)	0.392	53.3 (36.6)	50.7 (32.9)	1.000
Visuomotor integration[c]	28.1 (18.0)	30.1 (21.4)	0.891	31.0 (23.5)	30.0 (20.3)	0.960
Visual perception[c]	51.5 (19.8)	52.8 (24.6)	0.830	51.0 (17.7)	50.9 (22.6)	0.840
Visual memory[c]	35.3 (20.7)	23.4 (18.8)	0.086[b]	47.0 (30.9)	28.3 (17.8)	0.235
Executive functioning[c]	18.6 (24.0)	18.9 (24.2)	0.854	22.7 (12.7)	16.9 (24.6)	0.113
Behavioral outcome						
Behavioral problems[c]	46.8 (38.0)	39.1 (40.4)	0.587	61.5 (31.8)	37.1 (39.4)	0.218
Social behavior problems[e]	54.7 (28.8)	53.3 (35.4)	0.872	66.6 (19.8)	50.3 (32.4)	0.226
Total ADHD score[c]	43.0 (30.6)	44.9 (37.5)	0.810	66.0 (13.4)	39.6 (33.4)	0.101

b Neurodevelopmental outcome scores in children with and without SWC per recording

Outcome score	First recording			Second recording		
	SWC (*n* = 28)	no SWC (*n* = 14)	*p*	SWC (*n* = 39)	no SWC (*n* = 5)	*p*
Motor outcome						
Movement ABC total score[c]	38.7 (25.5)	46.3 (26.8)	0.415	41.4 (26.0)	42.0 (9.3)	0.926
Manual dexterity[f]	1.8 (0–4.5)	1 (0.5–3.4)	1.000	1.5 (0.5–3.6)	1.5 (0.3–4)	0.898
Ball skills[f]	2.5 (1.5–4.5)	2.8 (0.6–5.8)	0.919	2.3 (1.0–4.1)	3.0 (1.0–6.3)	0.619
Static and dynamic balance[f]	0.0 (0.0–0.0)	0.5 (0.0–1.5)	0.508	0.0 (0.0–1.5)	0.8 (0.1–1.8)	0.521
DCDQ 2007 total score[d]	64.9 (7.2)	64.1 (8.7)	0.965	65.2 (7.1)	61.8 (9.6)	0.405
Cognitive outcome						
Total IQ score	103.6 (8.9)	96.1 (9.9)	0.022[a]	101.0 (10.1)	103.8 (14.6)	0.626
Verbal IQ score	104.3 (11.0)	98.3 (12.0)	0.125	102.5 (12.1)	105.6 (18.9)	0.643
Performance IQ score	101.9 (13.3)	93.8 (11.3)	0.067[b]	99.2 (13.5)	100.5 (10.4)	0.833
Selective attention[c]	42.3 (27.9)	33.2 (24.9)	0.382	39.4 (27.0)	41.8 (20.5)	0.615
Attentional control						
Same world[c]	55.7 (29.0)	49.0 (29.9)	0.533	55.8 (28.5)	50.4 (38.3)	0.774
Opposite world[c]	45.3 (26.7)	43.9 (33.3)	0.814	47.5 (29.8)	30.8 (28.0)	0.216
Verbal learning[c]	59.0 (29.7)	50.0 (34.4)	0.527	57.6 (32.1)	58.3 (32.3)	1.000
Long-term verbal memory[c]	54.0 (31.3)	42.0 (33.4)	0.368	50.0 (33.2)	58.8 (34.2)	0.624
Visuomotor integration[c]	31.1 (19.8)	24.2 (17.9)	0.324	29.7 (19.3)	33.2 (30.3)	0.971
Visual perception[c]	57.1 (18.6)	40.1 (24.7)	0.049[a]	50.1 (21.2)	56.0 (27.4)	0.385
Visual memory[c]	34.5 (22.0)	19.1 (9.3)	0.090[b]	30.5 (21.2)	32.3 (12.5)	0.598
Executive functioning[c]	18.3 (25.4)	19.7 (20.8)	0.338	18.6 (24.0)	10.4 (17.1)	0.216
Behavioral outcome						
Behavioral problems[c]	42.4 (39.6)	45.2 (38.5)	0.793	43.9 (39.1)	13.0 (29.1)	0.133
Social behavior problems[e]	50.3 (31.9)	62.6 (31.0)	0.342	53.5 (31.1)	42.2 (36.2)	0.326
Total ADHD score[c]	44.9 (34.8)	41.7 (32.1)	0.827	44.6 (33.1)	28.0 (29.5)	0.273

Data are expressed as means (SD) or medians (p25 to p75). Higher scores represent better performance on the subtests, except for manual dexterity, ball skills, static and dynamic balance, executive functioning, and all behavioral outcome scores. DCDQ, Developmental Coordination Disorder Questionnaire; aEEG, amplitude-integrated electroencephalography; CNV, continuous normal voltage; DNV, discontinuous normal voltage; BS, burst suppression; SWC, sleep-wake cycling. [a] $p < 0.05$. [b] $p < 0.1$. [c] Percentile scores. [d] Scaled score; higher scores represent a better performance. [e] Scaled score; higher scores represent a worse performance. [f] Raw scores; higher scores represent a worse performance.

Table 4. Correlations between aEEG amplitude centiles of the first and second recording and outcome scores in preterm-born children

Outcome score	First recording						Second recording					
	mean p5		mean p50		mean p95		mean p5		mean p50		mean p95	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Motor outcome												
Movement ABC total score	–	–	–	–	–	–	–	–	–	–	–	–
Manual dexterity	–	–	–	–	–	–	–	–	–	–	–	–
Ball skills	–	–	–	–	–	–	–	–	–	–	–	–
Static and dynamic balance	–	–	–	–	–	–	–	–	–	–	–	–
DCDQ 2007 total score	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive outcome												
Total IQ score	–	–	–	–	–	–	–	–	–	–	–	–
Verbal IQ score	–0.381	0.017*	–	–	–	–	–	–	–	–	0.318	0.040*
Performance IQ score	–	–	–	–	–	–	–	–	0.254	0.096	–	–
Selective attention	–	–	0.347	0.026*	0.277	0.080	–	–	0.283	0.062	–	–
Attentional control												
Same world	–	–	–	–	–	–	–	–	–	–	–	–
Opposite world	–	–	–	–	–	–	–	–	–	–	–	–
Verbal learning	–0.275	0.091	–	–	–	–	–	–	–	–	–	–
Long-term verbal memory	–	–	–	–	–	–	–	–	–0.334	0.033*	–	–
Visuomotor integration	–	–	–	–	–	–	–	–	–	–	–	–
Visual perception	–	–	–	–	–	–	–	–	–	–	–	–
Visual memory	–	–	–	–	–	–	–	–	–	–	–	–
Executive functioning	–	–	–	–	–	–	–	–	–	–	–	–
Behavioral outcome												
Behavioral problems	–	–	–	–	–	–	–	–	–	–	–	–
Social behavior problems	–	–	–	–	–	–	–	–	–	–	–	–
Total ADHD score	–	–	–	–	–	–	–	–	–	–	–	–

Positive correlations indicate better outcome. Correlations are adjusted for clinical factors. * $p < 0.05$. DCDQ, Developmental Coordination Disorder Questionnaire; aEEG, amplitude-integrated electroencephalography; –, not significant.

BS (percentiles: 35.3 vs. 23.4, $p = 0.086$). Including GA in the model did not change the levels of significance.

There were no differences in behavioral outcomes between the aEEG background patterns.

Second Recording

No outcome measures were associated with the aEEG.

Presence of Cyclicity in Relation to Outcomes

We found that the total IQ was higher when cyclicity was present within the first 48 h after birth (mean 104, SD 8.9, vs. mean 97, SD 9.6; $p = 0.05$). In addition, scores on visual perception were higher (percentile: 57.1 vs. 40.1, $p = 0.049$). No confounders were found for these associations. In addition, we found that scores for visual memory were higher in the presence of cyclicity (percentile: mean 34.5 vs. mean 19.1, $p = 0.090$). The presence of cyclicity was not associated with behavioral or motor outcomes.

The presence of cyclicity in the second aEEG was not associated with outcomes.

Epileptic Activity

Since only 1 neonate had EA, we could not analyze the value of EA in predicting neuropsychological outcomes.

aEEG Amplitude Centiles in Relation to Outcomes

In both the first and the second recordings we found a few significant, albeit contrary, correlations between aEEG amplitude centiles and cognitive outcomes. We found no significant associations between aEEG amplitude centiles and behavioral or motor outcomes. The correlations are shown in Table 4 and were adjusted for possible confounders.

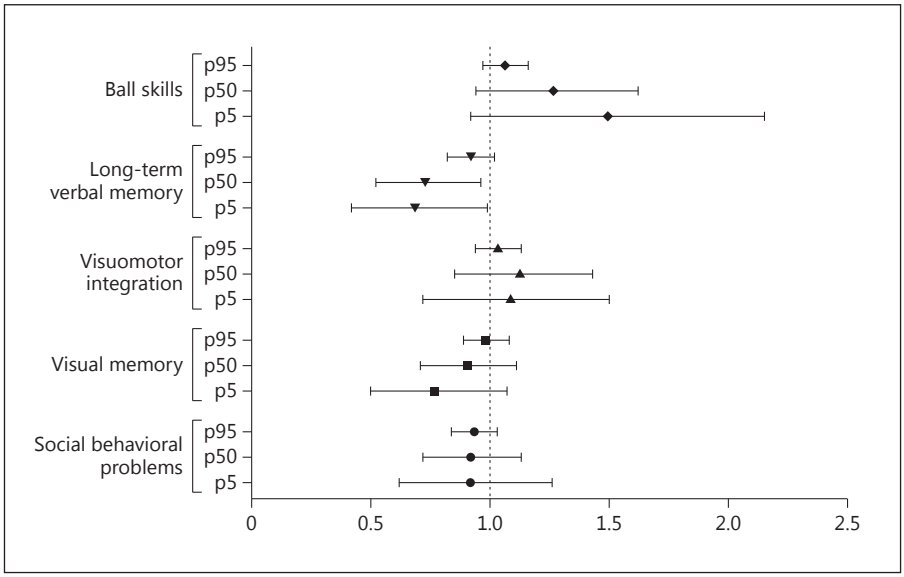

Fig. 2. The odds ratios (OR) of amplitude-integrated electroencephalography (aEEG) amplitude centiles of the first recording with regard to outcomes. Selection of outcome variables for which more children obtained abnormal scores than could be expected (>15%). OR > 1.0 reflect a statistically significant increase in the risk of abnormal outcomes.

The Value of aEEG Centiles in Predicting Outcomes

As depicted in Figure 2, during the first 48 h after birth, the mean 5th aEEG amplitude centile was predictive of long-term verbal memory, with an OR of 0.65 (95% CI 0.42–0.99, $p = 0.044$), as was the mean 50th aEEG amplitude centile, with an OR of 0.71 (95% CI 0.52–0.96, $p = 0.025$). There were no confounding factors for the associations between aEEG amplitude centiles and categorical outcomes.

Discussion

This study demonstrated that, in relatively healthy preterm infants, the value of aEEG in predicting neuropsychological outcomes at early school age is limited. BS was not associated with poorer outcomes. Cognition was better if cyclicity was present shortly after birth, with better scores for visual perception and total IQ. Calculating aEEG amplitude percentiles had no added value in predicting outcomes in this study in relatively healthy preterm infants. The predictive value of aEEG amplitude centiles in the form of OR was clinically irrelevant.

Previous studies investigating the value of early aEEG patterns in predicting long-term outcomes of preterm infants reported that abnormal aEEG soon after birth were associated with poorer outcomes at 2 and 3 years [4, 5]. At 2 years, the best predictor of poor outcomes was a BS pattern [4]. Abnormal scores on aEEG patterns within the first 2 weeks after birth were predictive of adverse outcomes at the age of 3 years [5]. We assessed aEEG background patterns, cyclicity, and EA separately. We only found an association between the presence of cyclicity during the first 48 h and functional outcome. The difference with previous studies is most likely related partly to our excluding the infants who had died. The previous studies did include infants who had died, which amounted to as much as 25% of their study population. In our opinion, it is more useful to know the predictive value of aEEG for surviving children, because aEEG is not a part of clinical decision-making, i.e., aEEG is not taken into account in the discussion about ending or continuing treatment. In contrast to previous studies, we also excluded infants with a large IVH, because it is known to influence both the background patterns of aEEG [20] and neurological outcomes. The predictive value of aEEG may therefore be larger in more severely ill infants with more intracranial abnormalities. Because we were particularly interested in whether aEEG could also contribute to predicting neurodevelopmental outcomes in infants without overt and serious brain lesions, we chose to limit our study to relatively healthy infants. Our findings have to be understood with this in mind.

Another important difference with the previous studies was the age at follow-up. Between the ages of 2 and 7 years, children experience an increasing number of developmental challenges. At early school age children experience more "nurturing" influences than do children aged 2–3 years. Ford et al. [22] reported that the environment in which preterm-born children develop determines to

some extent their outcomes. This may be another explanation for the differences of our present findings in comparison to those of previous studies.

Overall, the performance of our study population was better in almost all aspects of neuropsychological outcomes in comparison to those of other studies [23]. Few children obtained abnormal motor and IQ scores. This made it more challenging to determine the value of aEEG in predicting abnormal outcomes. Although our study population obtained abnormal scores on behavioral outcomes more often than the norm population, we found that aEEG did not predict behavioral outcomes. This may be explained by the fact that the cause of behavioral problems is multifactorial rather than being associated solely with prematurity.

In addition to looking at aEEG background patterns and cyclicity separately, we extended our study by investigating whether a quantitative analysis of the aEEG had added value in predicting outcomes [8]. Surprisingly, we found a few, albeit contrary, associations between aEEG centiles and outcomes. We only found borderline significant associations between the first aEEG and outcomes, and thus aEEG recordings directly after birth seem to have the greatest value in predicting outcomes. This is in line with previous studies investigating the value of aEEG assessment in preterm infants [4, 5, 21]. The predictive value may be limited, because several clinical conditions, e.g. sepsis or sedation, may influence the background activity [24–26].

We recognize several limitations. First, due to this being a single-center study with a small sample, we acknowledge that our results should be interpreted with caution and regarded as a preliminary, but no less important, indication. Second, we had to exclude 11 children because their parents declined to participate in the follow-up study or they were lost to follow-up, which was the case in more than 20% of the original study population. Unfortunately, due to excluding children from the cohort and the relatively large number of refusals to participate, our study was a little underpowered for some analyses. Third, the population was relatively healthy and the duration of the aEEG recordings relatively short. This might complicate comparability of the results, although we previously reported that aEEG amplitude centiles do not change during the first 5 days after birth in preterm infants [8, 27]. Even so, the sample size and the length of recording time, particularly during the first hours after birth, need to be expanded in future studies before any definite conclusions can be drawn. Starting to record EEG directly after birth and for a longer period of time will also provide information about the exact emergence of cyclicity. The time of onset of cyclicity might even be a better predictor of outcomes. Finally, because we performed an explorative study, we did not make corrections for multiple comparisons. Therefore some findings may be explained by chance.

In conclusion, this study showed that in relatively healthy preterm infants the value of aEEG in predicting long-term neuropsychological outcomes is limited. A more depressed aEEG is not associated with poorer outcomes. The presence of cyclicity directly after birth is associated with better cognition. Motor and behavioral outcomes are not associated with aEEG patterns. Quantitative analysis of aEEG has no added value.

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Disclosure Statement

None reported.

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